THE EFFECT OF USING COMBINATION CHEMOTHERAPY IN COLORECTAL CANCER IN INDIA: A SINGLE INSTITUTE SURVEY

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Short Title:- Efficacy of combination chemotherapy in colorectal cancer

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Summary

The incidence of colorectal cancer in India is on upward swing due to the change in dietary habits. This study was done to evaluate the efficacy and toxicity of 5– fluorouracil monotherapy and 5-fluorouracil +levamisole regimens. In this study, colorectal cancer patients treated with adjuvant chemotherapy from 1997 to 2001 were included and followed up for a period of five years. The efficacy of the commonly used regimens was compared in terms of five year disease free survival. The various toxicity seen during the adjuvant chemotherapy administration was recorded in either group. The three and five year disease free survivals of 5–fluorouracil monotherapy regimen were 42% and 32% respectively in stage B. The 5-fluorouracil +levamisole regimen had a disease

free survival of 46% and 38 % in stage B at three and five years respectively. In stage C, the disease free survival at three and five year were 22% and 10% in 5- fluorouracil treated group whereas it was 24% and 16% in 5-fluorouracil with levamisole treated group at similar time interval. The incidence blood dyscrasia and abnormal liver function test were higher in 5-fluorouracil monotherapy group. We conclude that 5-fluorouracil monotherapy had equal disease free survival and slightly more toxic compared to 5-fluorouracil and levamisole combination in stage B & stage C colorectal cancer.

Key words: - Adjuvant chemotherapy, Disease free survival, 5-fluorouracil , 5- fluorouracil+ levamisole

Introduction

Colorectal cancer accounts for 10-15% of all cancers and is the second leading cause of cancer related death in western countries though its incidence is less in Indian set up. [1]]Incidence of cancer in male: female is 6.7: 5. 5 per 100, 000 population in India. Risk factors for the colorectal cancer are dietary habits and familial adenomatous polyposis. [2] Due to various reasons, the incidence of colorectal cancer is on increasing trend in India. [3] Surgery is the primary modality for curative intent, and it varies according to the site of tumor like hemicolectomy (depending on right or left sided colon cancer) and abdominoperineal resection in colorectal cancer. Systemic chemotherapy plays a major role in various stages of colorectal cancer. Chemotherapy and radiotherapy have a clear role in adjuvant therapy and for symptom palliation in advanced disease. [4] There are various regimens instituted, in which fluorouracil forms an effective chemotherapeutic drug for this cancer, along with levamisole, leucovorin calcium, oxaliplatin, capecitabine, irinotecan combinations.

Despite recent advances in chemotherapeutic treatment, great numbers of deaths occur each year from the disease as well as due to the adverse effects of anticancer drugs. There are enough data regarding the efficacy of various regimens, used in different stages of colorectal carcinoma among western population. [5, 6 & 7] The risk factors in our patient population is different from the risk factors in western population, hence the efficacy. [3] To best of our

knowledge, there is lack of data about the efficacy and toxicity of the same in Indian patient population. Hence a study was planned to know the efficacy and toxicity of commonly used adjuvant chemotherapeutic regimens in different stages of colorectal cancer in terms of disease free survival in our hospital set up during 1997-2001.

Materials and methods

Patients of either sex, diagnosed to have colorectal cancer based on histopathology were included in this retrospective study. The study was approved by the Kasturba Hospital Ethics Committee.The study was conducted in Shri Shiridi Sai Saba Cancer Institute, Manipal (A wing of Kasturba Hospital, Manipal, India) which is a referral hospital for South Karnataka, neighbouring states such as Goa and northern districts of Kerala during 1997-2001. We have seen 304 patients of colorectal cancer of Dukes stage A, B, C and D (table 1). [8] We have included 91 patients [Dukes stage B (62) and C (29)] in our study who completed one chemotherapy regimen and excluded patients of dukes stage A and D. We had 44 patients in 5-fluorouracil monotherapy arm (30+14 in stage B & C respectively) and 47 patients in 5-fluorouracil and levamisole combination arm (32+15 in stage B & C respectively).The patients in either arm were comparable with respect to age, stage and prognostic factors, dose, duration of therapy. The patients in 5 –FU monotherapy arm received 500mg i.v bolus for five days in a week. In the other arm, levamisole was given in a dose of 150mg twice daily for three days during 5-FU administration. This treatment was repeated every 4 weeks for six month period in both arms. The gastrointestinal manifestations, alopecia, haematological, hepatic and renal abnormalities were monitored during the monthly infusions of chemotherapy and one month after the completion of chemotherapy.

Patients were followed up for 5 years from the day of completion of chemotherapy. The necessary informations such as staging of cancer (modified Astler –Coller Dukes system), type of adjuvant chemotherapy received were collected from the hospital medical records for each patient. The status of the patient after receiving chemotherapy was inquired by writing self-addressed post card to

the patient and patient's attenders, if it was not available on case sheet. Efficacy was evaluated by using three and five year disease free survival (DFS i.e. the length of time after treatment for a specific disease during which a patient survives with no sign of the disease) for the commonly used regimens such as 5-fluorouracil monotherapy (5-FU) and 5-FU + levamisole (5-FU+lev) as this regimen was commonly used in our hospital set up between 1997-2001. The selection of the treatment regimen was mainly based on staging, physician and patient preference.

Table 1: Dukes classification of colorectal cancer

Dukes Stage	Features
Stage A	Tumor restricted to, but not through the bowel wall
Stage B	Penetration through the bowel wall
Stage C	Spread to the local lymph nodes
Stage D	Distant metastasis

Statistical Analysis

Three year and five year disease free survival, in various stages (B and C) as well as for various chemotherapeutic regimens (5-FU, 5-FU+lev) were calculated by using survival curves, which plot percent survival as a function of time using the method of Kaplan and Meier (Graph-pad Prism statistical software package). The percentage of survival were obtained by drawing a perpendicular line from X axis at the interval of 36 months (3years) and 60 months (5 years) to the curve and drawing a horizontal line from that point to Y axis.

Results

In this study we have analyzed the data of 91 patients with colorectal cancer of stage B and stage C, who were treated during and completed one chemotherapeutic regimen 1997-2001.

These patients were chosen from the pool of 304 patients who had been diagnosed and treated during this same period. Rests of the patients were either of stage A, stage D or stage B& C who discontinued the treatment because of socio economical reasons. The patient demographic profiles were given in table 2.

Table 2 showing patient characteristics (Values in parenthesis shows the percentage)

Patient characteristics		Number
Total number of patients		91
Male to female ratio		60:31
Age distribution (In years)	31-40	14(15.38)
	41-50	18(19.78)
	51-60	28(30.76)
	61-70	18(19.78)
	Miscellaneous	13(14.28)
Patients in different stages	Dukes B	62(68.13)
	Dukes C	29(31.87)

Efficacy of different chemotherapeutic regimens:

We have analyzed the data of patients who have been treated in our hospital for colorectal cancer during 1997-2001.The overall three and five year disease free survival was 44% and 38% in stage B & 20% and 10 % in stage C which was statistically significant (fig 1, $P<0.04$). The three and five year disease free survivals in 5-FU treated group of stage B patients were 42% and 32% respectively (fig 2). The 5-FU +levamisole combination had a disease free survival of 46% and 38% at three and five years respectively in stage B. There was no statistical significant difference between the two treatment groups even though little difference between the two groups **(**$P= 0.065$ and 0.085 between 5-FU and 5 –FU + lev at three and five years interval).

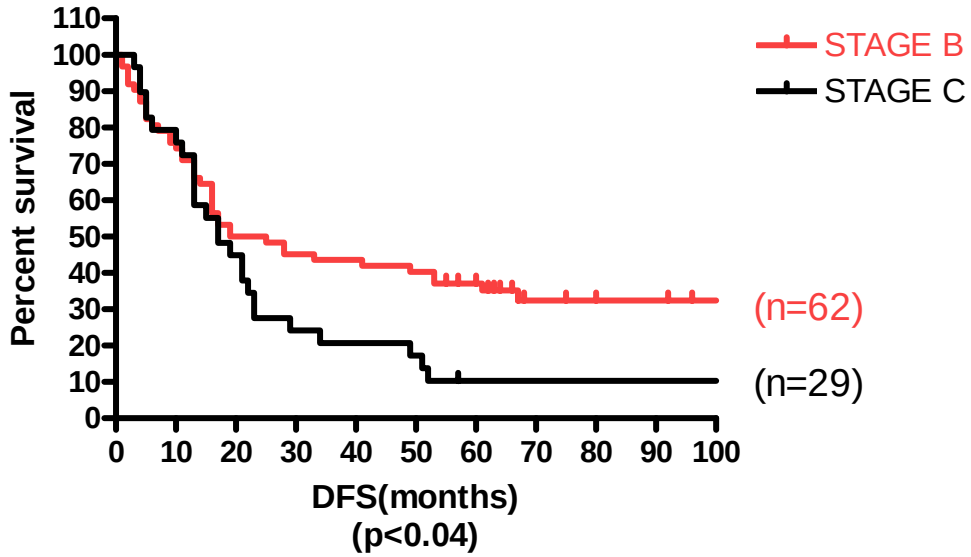

Fig 1: Stagewise disease free survival in different stages of colorectal cancer

The three and five year disease free survivals in 5-FU treated group of stage B patients were 42% and 32% respectively (fig 2). The 5-FU +levamisole combination had a disease free survival of 46% and 38% at three and five years respectively in stage B. There was no statistical significant difference between the two treatment groups even though little difference between the two groups **(**P= 0.065 and 0.085 between 5-FU and 5 –FU + lev at three and five years interval).

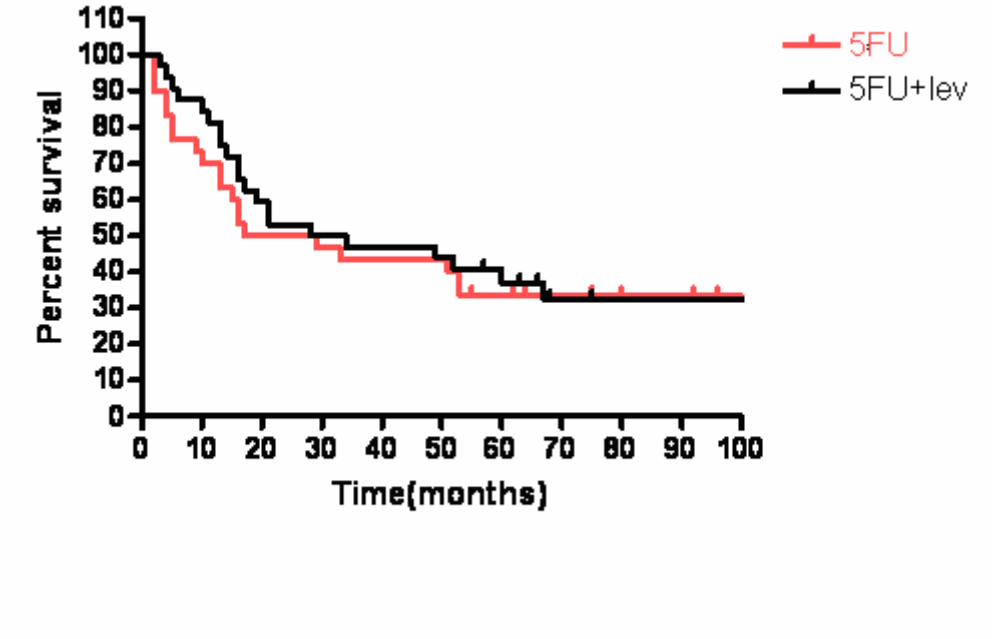

Fig 2: Disease free survival in stage B treated with two regimens [(P = 0.065 and 0.085 between 5-FU and 5 –FU + lev at three and five years interval), (5-FU=30, 5-FU+lev=32)].

Twenty two percent of patients treated with 5-FU were free from recurrence at three years and 10% were free of recurrence at five years in stage C. 5-FU + levamisole treated patients had a disease free survival of 24% &16% at three and five years respectively in stage C, with no statistically significant difference between B& C. (fig 3, P =0.068 and 0.059 between 5-FU and 5 –FU + lev at three and five years interval).

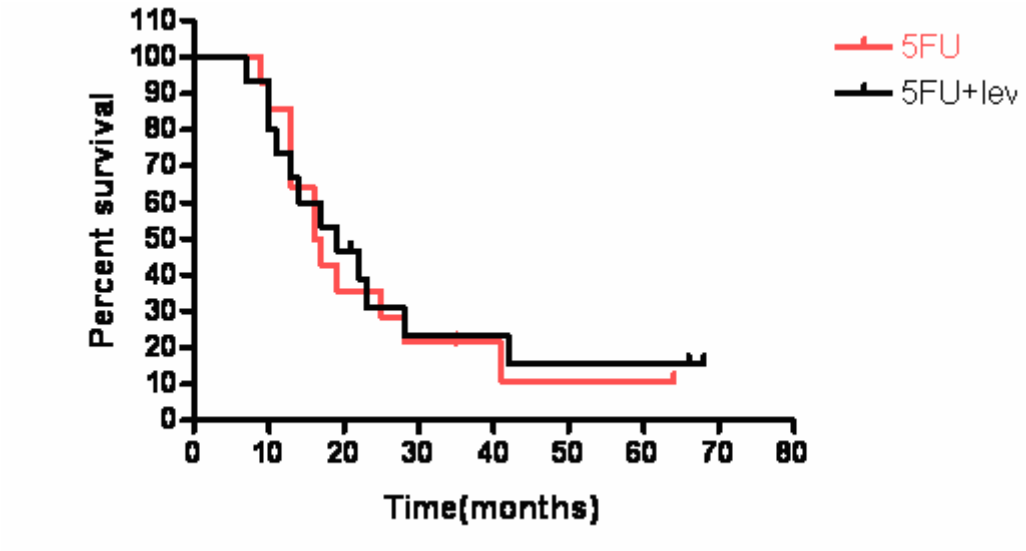

Fig 3: Disease free survival in stage C treated with two regimens.
[(P =0.068 and 0.059 between 5-FU and 5 –FU + lev at three and five years interval), (5-FU=14, 5-FU+lev=15)]

The three common adverse effects seen with these groups were blood dyscrasia (28.05 vs.
22.99%), LFT abnormalities in the form of elevated ALT, AST, hypoalbuminemia 23.17 vs. 20.69%) and GIT manifestation in the form of nausea, vomiting, diarrhoea, constipation (23.17% vs. 25.29%) in 5- fluorouracil and 5-fluorouracil+ levamisole combination respectively.

Discussion

The selection of adjuvant chemotherapeutic regime for a particular patient depends on many factors like staging of the cancer, other treatment modalities received, the tolerability and affordability for a particular regime in a given set up. Substantial progress has been made in the identification of new forms of treatment for colorectal cancer. [9, 10] Patients with metastatic disease are living twice as long as there were one decade ago. The use of adjuvant chemotherapy has increased the likelihood of cure by 30% among patients with stage III which is also called as Dukes stage C. [5, 8] In the last decade, 5-FU and leucovorin combination was used as the principle adjuvant chemotherapy regime for colon

cancer of Stage III. Patients with stage II colon cancer (Dukes B) were encouraged to participate in the on-going trials because adjuvant therapy has not yet proved to offer a survival benefit. [11] For rectal cancers, post operative 5-FU based chemotherapy combined with irradiation should be the standard clinical approach for stage II and stage III disease because of its proven decrease in local recurrence, cancer related deaths and overall mortality. [12] In our hospital set-up, oxaliplatin and FolFox regimens are used in the adjuvant treatment of stage III currently. Since 5-fluorouracil and levamisole regimens were being used during 1997-2001 and oxaliplatin, FolFox regimens were just started showing positive results during that time, we included patients who have received 5-fluorouracil and levamisole regimens and followed them for five years.

We have not evaluated the efficacy of other regimens were not analysed because of fewer numbers of cases. DFS after three years of median follow up is considered as an appropriate endpoint in colorectal cancer. [13] This can also be considered as surrogate to five year overall survival in colorectal cancer hence we used this parameter to evaluate the efficacy of the above mentioned regimens. [14] Various clinical trial groups have shown that addition of levamisole to 5-fluorouracil do not improve the recurrence rates eventhough immunostimulatory effect of levamisole was thought to enhance the therapeutic efficacy of 5-fluorouracil. [5, 6] The efficacy of both the regimens found to better than our study. Some studies have shown that 5-fluorouracil+levamisole was slightly better than 5 fluorouracil monotherapy. [7] The reason given for the slight edge of the combination could be due to higher dose of 5-fluorouracil and the number of patients enrolled for the study in these trials.[15] In the stage B and stage C disease, the five year overall survival was found to be in the range of 70-80% and 35-60% respectively which can be comparable to three year disease free survival.[2,14] Our study revealed that the efficacy of two regimens were more or less similar from efficacy point of view in terms of three year disease free survival (42% and 22% in stage B & stage C with 5-fluorouracil monotherapy and 46% and 24 % in 5-fluorouracil combined with levamisole respectively). The recurrence rates were much higher in our patients (opposite of disease free survival) compared to QUASAR collaborative group. [15]

We have not considered grading of the tumor, lymph vascular involvement and number of lymhnodes involved. We think this has affected the outcome of the study. Had we randomized on these grounds, the efficacy could be near to the western literature. This was the weak link in our study. Since the efficacy data in Indian patient population is lacking with these regimens, this could be a valuable data in developing countries like India and other Asian countries. We compared our results with the western literature since published data with these regimens are not available in similar settings.

The combination regimen had less incidence of haematological and hepatic abnormality when compared to 5-fluorouracil monotherapy. But the combination regimen had higher incidence of gastrointestinal disturbances. The increased incidence of gastrointestinal toxicity in levamisole treated patients was documented in the literature. [16]

We conclude that 5-fluorouracil monotherapy is equally effective as 5-fluorouracil and levamisole combination in terms of efficacy in stage B & stage C colorectal cancer. Larger sample size, randomization in terms of grading, lymhovascular invascular invasion and nodal involvement could have thrown more information regarding the benefit of levamisole in the combination of 5- fluorouracil in the treatment of stage B & stage C colorectal cancer.

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